Sussex Research Online

A retrospective observational study to determine baseline characteristics and early prescribing patterns for patients receiving Alirocumab in UK clinical practice

Article (Published Version)

Reynolds, Tim, Carey, Peter, George, Jacob, Konidaris, Gerasimos, Narayanan, Deepa, Ramachandran, Sudarshan, Saunders, Luke, Viljoen, Adie and Ferns, Gordon (2019) A retrospective observational study to determine baseline characteristics and early prescribing patterns for patients receiving Alirocumab in UK clinical practice. Drugs - Real World Outcomes, 6 (4). pp. 205-213. ISSN 2199-1154

This version is available from Sussex Research Online: http://sro.sussex.ac.uk/id/eprint/88656/

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:
Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

http://sro.sussex.ac.uk

Drugs - Real World Outcomes (2019) 6:205–213
https://doi.org/10.1007/s40801-019-00166-7

SHORT COMMUNICATION

A Retrospective Observational Study to Determine Baseline Characteristics and Early Prescribing Patterns for Patients Receiving Alirocumab in UK Clinical Practice

Tim Reynolds[1] · Peter Carey[2] · Jacob George[3] · Gerasimos Konidaris[4] · Deepa Narayanan[5] · Sudarshan Ramachandran[6] · Luke Saunders[7] · Adie Viljoen[8] · Gordon Ferns[9]

Published online: 18 November 2019
© The Author(s) 2019

Abstract

Background Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) and has been previously shown, in the phase III ODYSSEY clinical trial program, to provide significant lowering of low-density lipoprotein cholesterol (LDL-C) and reduction in risk of major adverse cardiovascular events. However, real-world evidence to date is limited.

Objective The primary objective was to describe baseline characteristics, clinical history, and prior lipid-lowering therapy (LLT) use of patients initiated on alirocumab in UK clinical practice following publication of health technology appraisal (HTA) body recommendations. Secondary objectives included description of alirocumab use and lipid parameter outcomes over a 4-month follow-up period.

Methods In this retrospective, single-arm, observational, multicenter study, data were collected for 150 patients initiated on alirocumab.

Results Mean (standard deviation; SD) age of patients was 61.4 (10.5) years and baseline median (interquartile range; IQR) LDL-C level was 4.8 (4.2–5.8) mmol/l. Alirocumab use occurred predominantly in patients with heterozygous familial hypercholesterolemia (HeFH) ($n = 100/150$, 66%) and those with statin intolerance ($n = 123/150$, 82%). Most patients started on alirocumab 75 mg ($n = 108/150$ [72%]) and 35 (23.3%) were up-titrated to 150 mg. Clinically significant reductions in atherogenic lipid parameters were observed with alirocumab, including LDL-C (median [IQR] change from baseline, − 53.6% [− 62.9 to − 34.9], $P < 0.001$).

Conclusion This study highlights the unmet need for additional LLT in patients with uncontrolled hyperlipidemia and demonstrates the clinical utility of alirocumab in early real-world practice, where dosing flexibility is an important attribute of this therapeutic option.

1 Introduction

Elevated LDL-C is a risk factor for cardiovascular disease (CVD), and its role in the pathogenesis of atherosclerosis is well established [1]. Importantly, it is the only lipid parameter shown to reduce the rate of CVD via targeted therapeutic intervention [2–5].

Low-density lipoprotein receptors (LDLRs) are present on the surface of all cells, including hepatocytes, which are responsible for clearing circulating LDL-C. PCSK9 is an enzyme that binds to and promotes the degradation of LDLR, reducing LDL-C clearance [6, 7]. Alirocumab, a fully human immunoglobulin G1 monoclonal antibody, binds with high affinity and specificity to PCSK9, inhibiting its binding to and intracellular degradation of LDLR; this in turn increases the amount of LDLR available to clear LDL-C, lowering plasma LDL-C concentrations [8–10].

The efficacy and safety of alirocumab have been extensively investigated in the ODYSSEY phase III clinical trial program, including patients with HeFH as well as those with non-familial high-risk hypercholesterolemia [11]. Alirocumab has demonstrated clinically meaningful LDL-C reductions in patients with a range of genetic variants causative of HeFH [6, 7].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40801-019-00166-7) contains supplementary material, which is available to authorized users.

✉ Gordon Ferns
G.Ferns@bsms.ac.uk

Extended author information available on the last page of the article

Key Points

This study is the largest multicenter study of alirocumab in real-world UK clinical practice.

Early alirocumab use post-issuance of health technology body recommendations predominantly occurred in patients with HeFH. Uptake of a novel therapeutic in this high-risk patient group and those with a large degree of statin intolerance highlights the previously unmet need for additional lipid-lowering treatment options.

Flexibility in dosing and the ability to adjust dose based on response and acceptability may be important when initiating a new treatment; a higher degree of alirocumab use at initiation with the 75 mg strength than the 150 mg strength was reported.

Clinically significant reductions in the lipid parameters, LDL-C, non-HDL-C, and total cholesterol observed with alirocumab in real-world practice were consistent with the phase III trial program.

Results from the ODYSSEY trials supported the marketing authorization of alirocumab in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet. Alirocumab is indicated for use in combination with a statin, or statin with other lipid-lowering therapies (LLTs), in patients unable to attain LDL-C goals with the maximum tolerated dose of a statin alone or in combination with other LLTs in patients who are statin intolerant or for whom a statin is contraindicated [9].

The usual starting dose of alirocumab is 75 mg administered subcutaneously once every 2 weeks (Q2W); however, patients requiring larger LDL-C reduction (> 60%) may be started on 150 mg Q2W or 300 mg monthly. Only the 75 mg and 150 mg strengths were available in the UK during the observation period of this study. Ongoing treatment is individualized based on patient characteristics and response [9].

Following receipt of marketing authorization, alirocumab has been assessed by UK HTA bodies. The National Institute of Health and Care Excellence (NICE) recommends alirocumab as an option for treating certain patients with primary hypercholesterolemia or mixed dyslipidemia on maximally tolerated LLT based on their prior CVD event history and LDL-C concentrations [12]. The Scottish Medicines Consortium (SMC) recommends specialist use only of alirocumab in patients at high cardiovascular risk, e.g., patients with HeFH and LDL-C ≥ 5.0 mmol/l, for primary prevention of cardiovascular events or patients with HeFH and LDL-C ≥ 3.5 mmol/l, for secondary prevention of cardiovascular events or patients at high risk due to previous cardiovascular events and LDL-C ≥ 4.0 mmol/l or patients with recurrent/polyvascular disease and LDL-C ≥ 3.5 mmol/l [13].

Subsequent to marketing authorization and HTA body recommendations, it is of interest to describe alirocumab use across UK clinical practice to understand the baseline profile of patients and prescribing patterns supporting future HTA discussion since, at publication, available evidence was from studies held in one or two UK centers only [14–16].

The primary objective of this study was to describe baseline characteristics, clinical history, and prior LLT use of patients initiated on alirocumab in early UK clinical practice, following publication of HTA body recommendations. Secondary objectives were to describe alirocumab use (starting dose and titration patterns), LLT use, and lipid measurements over a 4-month post-initiation period. Change in lipid parameters from baseline to post-initiation was also observed as an exploratory end point.

2 Methods

This retrospective, observational, single-arm study was conducted in ten National Health Service (NHS) centers across the UK. Sites were chosen from different geographical locations across England, Wales, and Scotland.

Anonymized patient-level data, corresponding to a predefined core data set, were collected from electronic medical notes and paper charts and entered into a database. The database was compliant with the Code of Federal Regulations 21, Part 11 [17], and approved for use in the NHS setting.

The study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) [18], and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice [19], in accordance with local regulations, including local data protection regulations.

The study included patients aged ≥ 18 years initiated on alirocumab between May 2016 and July 2017. Patients who initiated on alirocumab ≥ 4 months before the date of data collection were included and were required to have made ≥ 1 contact with the site within the post-initiation period.

Exclusion criteria were: enrollment in a trial while taking alirocumab, previous enrollment in PCSK9 inhibitor (PCSK9i) trial, pregnancy, or secondary causes of dyslipidemia (e.g., drug-induced, hypothyroidism, renal failure, nephrotic syndrome, and excessive alcohol usage).

To avoid selection bias, patients were recruited in reverse consecutive order from the last eligible patient seen during the most recent clinic visit. A minimum target of 5 and a maximum of 30 eligible patients per center were chosen pragmatically to ensure geographical representation and to minimize potential for center bias (Online Resource 1). Data

heterogeneity was evaluated using one-way analysis of variance (ANOVA) comparing baseline LDL-C levels between sites.

Data for cardiovascular event and statin-use history were collected at any point between primary hyperlipidemia diagnosis and alirocumab initiation. The most recently available measurements within a 6-month period prior to the initiation of alirocumab were collated for the remainder of baseline variables. Different data collection time periods were used for the various variables based on feasibility of being able to collect these data in routine real-world clinical practice. Additionally, HeFH diagnosis was made on clinical or genetic grounds since not all centers had access to genotyping facilities.

The post-initiation period was defined as the 4-month period following alirocumab initiation. Alirocumab starting dose, titration, and discontinuation, change in or discontinuation of LLT, and lipid parameters were collected over this period. Statistical methods for lipid parameter analyses can be found in Online Resource 2.

Treatment discontinuation was captured and reasons recorded as follows: lack of efficacy, difficulty with dosing, difficulty with device, adverse events (AEs), or unknown.

Descriptive statistics were calculated for quantitative and qualitative variables and analyzed using STATA v14.2 (StataCorp LLC, College Station, TX, USA). Although a descriptive study, it was estimated that a sample size of 138 patients would be required to achieve a precision for the main baseline parameter of interest (LDL-C), such that 95% confidence interval widths would be 0.5 mmol/l from the estimate of the mean assuming a standard deviation (SD) of 1.5 mmol/l. No formal power calculations for lipid outcomes were performed. Additionally, a post hoc analysis assessed time to up-titration from alirocumab 75 mg to alirocumab 150 mg.

3 Results

An analysis of between-center heterogeneity comparing baseline LDL-C levels between sites found no significant difference (one-way ANOVA, $P = 0.3$), allowing pooling of patient data across centers.

Baseline characteristics, medical history, and clinical history of the cohort ($n = 150$) prior to alirocumab initiation can be seen in Table 1. Mean age at baseline was 61.4 (SD: 10.5) years, and 74 (49.3%) patients were male. Two-thirds of patients had a HeFH diagnosis (either phenotype or genotype; $n = 100$ [66.7%]), 26 (17.3%) had primary non-familial hypercholesterolemia, and 24 (16.0%) had mixed dyslipidemia. Mean body mass index (BMI) was 29.3 (SD: 4.5), and 33 (37.5%) patients had a BMI of ≥ 30 kg/m^2. However, these data were only available for 88 patients. Twenty-seven (18.0%) had a diabetes diagnosis. Patients had a median of one prior cardiovascular event (range 0–12): 42 (28.0%) had previous myocardial infarction, 9 (6.0%) had unstable angina, and 10 (6.7%) had peripheral artery disease. Additionally, alirocumab was known to be prescribed within the NICE/SMC recommendations in 67% of patients ($n = 100$).

When considering previous hyperlipidemia-related treatment, patients had received a median of three statins since diagnosis (range 1–5; interquartile range [IQR] 2–4). Two-thirds ($n = 100$ [66.7%]) were, in the opinion of the treating physician, intolerant to ≥ 2 statins. The most common reason for discontinuing or changing statin dose was due to AE (17/37 [45.9%]; Table 2). Overall, background LLT remained unchanged between the pre- and post-initiation periods; however, these data were sparsely recorded across sites.

On alirocumab initiation, 72.0% ($n = 108$) of patients received alirocumab 75 mg. Thirty-five (23.3%) patients were up-titrated to 150 mg. Two (1.3%) patients were up-titrated to 150 mg and then subsequently down-titrated to 75 mg over the observation period (reason not captured). Median time to up-titration was 11.7 (range 4.0–16.0; IQR 8.0–12.9) weeks. Nineteen (12.7%) patients discontinued alirocumab, most commonly because of AEs (17/19 [89.5%]; Table 3).

Median (IQR) LDL-C at baseline was 4.8 [4.2–5.8] mmol/l (reported for 94 [62.7%] patients who did receive any alirocumab dose change prior to measurement of a paired post-initiation LDL-C value). A median reduction in LDL-C to 2.3 (IQR 1.7–3.1) mmol/l post-alirocumab initiation was observed for the overall group ($n = 94$), equating to a median change of –53.6% from baseline ($P < 0.001$) (Fig. 1). Significant median [IQR] reductions in LDL-C were also observed both for the subgroup of patients who received alirocumab 75 mg (− 50.0% [− 60.0 to − 32.8], $P < 0.001$) and those who received alirocumab 150 mg (− 60.2% [− 69.8 to − 50.3], $P < 0.001$) (Table 4). Changes in other lipid parameters over the observation period can be seen in Fig. 1. Clinically significant reductions in non-HDL-C and total cholesterol were observed ($P < 0.001$), in line with the strength of alirocumab administered (Table 4).

4 Discussion

This is the largest multicenter study of alirocumab in real-world UK clinical practice across a range of centers in the UK, following the publication of NICE and SMC recommendations. Alirocumab use occurred predominantly in patients with HeFH, who were known to be at high risk of cardiovascular complications compared with the general population [20]. This observation together with the high

Table 1 Baseline characteristics and medical history for UK patients initiated on alirocumab

Variable	Cohort ($N=150$)[a]
Diagnosis, *n* (%)	
Primary non-familial hypercholesterolemia	26 (17.3)
Mixed dyslipidemia	24 (16.0)
Primary HeFH (clinically or genetically defined)	100 (66.7)
Age, years	
Mean (SD)	61.4 (10.5)
Gender, *n* (%)	
Male	74 (49.3)
BMI, *n*	88
Overall BMI, mean (SD) kg/m^2	29.3 (4.5)
Underweight (16 to < 18.5 kg/m^2), *n* (%)	0 (0.0)
Normal (18.5 to < 25 kg/m^2), *n* (%)	16 (18.2)
Overweight (25 to < 30 kg/m^2), *n* (%)	39 (44.3)
Obese (≥ 30 kg/m^2), *n* (%)	33 (37.5)
Diabetes, *n* (%)	
Yes	27 (18.0)
Type 1	3 (11.1)
Type 2	24 (88.9)
No	123 (82.0)
Cardiovascular-related comorbidities, *n* (%)	
Chronic heart failure	4 (2.7)
Arrhythmia	4 (2.7)
Chronic kidney disease (stage II–ESRD), *n* (%)	14 (9.3)
Hypertension	67 (44.7)
Cardiovascular event history	
Number of previous events, median (range; IQR)[b]	1.0 (0–12; 0–1)
Myocardial infarction, *n* (%)	42 (28.0)
Ischemic stroke, *n* (%)	11 (7.3)
Hemorrhagic stroke, *n* (%)	1 (0.7)
Unstable angina, *n* (%)	9 (6.0)
Stable angina, *n* (%)	25 (16.7)
Peripheral arterial disease, *n* (%)	10 (6.7)
Cardiovascular revascularization procedure history, *n* (%)	
Coronary artery bypass graft	20 (13.3)
Percutaneous coronary intervention/percutaneous transluminal coronary angioplasty	23 (15.3)
Carotid	4 (2.7)
Femoral	5 (3.3)
Categorization per NICE/SMC criteria, *n* (%)	
Primary non-familial hypercholesterolemia or mixed dyslipidemia with high risk of cardiovascular disease and LDL-C > 4.0 mmol/l	12 (8.0)
Primary non-familial hypercholesterolemia or mixed dyslipidemia with very high risk of cardiovascular disease and LDL-C > 3.5 mmol/l	16 (10.7)
Primary HeFH without cardiovascular disease and LDL-C > 5.0 mmol/l	34 (22.7)
Primary HeFH with cardiovascular disease (either high-risk or very high risk) and LDL > 3.5 mmol/l	38 (25.3)
Did not fit NICE/SMC recommendations	36 (24.0)
Not known[c]	14 (9.3)

BMI body mass index, *CV* cardiovascular, *CVA* cerebrovascular accident, *CVD* cardiovascular disease, *HeFH* heterozygous familial hypercholesterolemia, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *NICE* National Institute of Health and Care Excellence, *PAD* peripheral arterial disease, *SMC* Scottish Medicines Consortium, *SD* standard deviation

[a]Unless otherwise stated; not all variables were available for all patients

[b]Events were defined as the following: myocardial infarction (MI), coronary artery by-pass graft (CABG), revascularization (PCI/PTCA, carotid or femoral), cerebrovascular accident (ischemic or hemorrhagic), unstable angina, and peripheral arterial disease (PAD). All data for revascularization procedures were reviewed on a case-by-case basis, and revascularization procedures (CABG, PCI/PTCA, 'revascularization-carotid,' 'revascularization-femoral') that occurred within 90 days of a defined CV event (MI, CVA-ischemic, CVA-hemorrhagic, unstable angina, PAD) were counted as the same event for analysis purposes

[c]Patients whose baseline LDL-C values were not available to categorize patients

level of statin intolerance recorded in this study highlights the previously unmet need for treatment options after the failure of conventional hyperlipidemia treatment.

The high median baseline LDL-C level of the cohort (4.8 mmol/l) suggested that most patients would be initiated on alirocumab 150 mg, according to recommendations in the Summary of Product Characteristics [9]. However, only 42 (28%) patients were initiated on the 150 mg strength. Additionally, given that most patients had a diagnosis of HeFH ($n=100/150$ [66.7%]), we observed less frequent up-titration from alirocumab 75 mg to 150 mg in the real world compared with some studies of these patients within the ODYSSEY phase III program [21]. Predominant initiation of alirocumab 75 mg compared with 150 mg may be attributed to clinician or patient preference, cautious prescribing because of limited experience of PCSK9i, or local prescribing guidelines implemented during the early period after the publication of HTA body recommendations. Despite the lower use of the higher strength of alirocumab (150 mg), a clinically significant reduction in LDL-C was observed, consistent with that seen in randomized clinical trials [11].

On alirocumab initiation, 108 (72.0%) patients received alirocumab 75 mg. Thirty-five (23.3%) patients were up-titrated to 150 mg. Two (1.3%) patients were up-titrated

Table 2 Prior lipid-lowering therapy use for UK patients initiated on alirocumab

Variable	Cohort ($N=150$)[a]
Patients with statin use since diagnosis	
Number of statins used since diagnosis, median (range; IQR)	3 (1–5; 2–4)
1, *n* (%)	25 (16.7)
2, *n* (%)	33 (22.0)
3, *n* (%)	41 (27.3)
4, *n* (%)	40 (26.7)
5, *n* (%)	11 (7.3)
Patients with known statin intolerance since diagnosis, *n* (%)	
Intolerant to no statins	27 (18.0)
Intolerant to ≥ 1 statin	123 (82.0)
Intolerant to ≥ 2 statins	100 (66.7)
Patients with lipid-lowering therapy use within 6 months prior to alirocumab initiation, *n* (%)	
None	56 (37.3)
≥ 1 lipid-lowering therapy	94 (62.7)
Statin	63 (42.0)
Ezetimibe	67 (44.7)
Fibrates	11 (7.3)
Other[b]	11 (7.3)
Patients with statin use within 6 months prior to alirocumab initiation, *n* (%)	63
Atorvastatin[c]	17 (27.0)
20 mg	2/17 (11.8)
40 mg	5/17 (29.4)
80 mg	7/17 (4.1)
Other	3/17 (17.6)
Rosuvastatin[c]	34 (54.0)
10 mg	5/34 (14.7)
20 mg	4/34 (11.8)
40 mg	11/34 (32.4)
Other	14/34 (41.2)
Simvastatin	0 (0.0)
Pravastatin	6 (9.5)
Fluvastatin	6 (9.5)
Statin regimen within 6 months prior to alirocumab initiation, *n* (%)	63
Once daily	50 (79.4)
Twice daily	2 (3.2)
Weekly	6 (9.5)
Other[d]	5 (7.9)
Patients receiving high-intensity statin within 6 months prior to alirocumab initiation, *n* (%)	41
Atorvastatin (80 mg)	7 (17.1)
Atorvastatin (20–80 mg)	14 (34.1)
Rosuvastatin (10–40 mg)	20 (48.8)
Simvastatin (80 mg)	0 (0.0)
Reason for lipid-lowering therapy discontinuation/dose change prior to alirocumab initiation, *n* (%)[e]	–
Statin changes	37
Lack of efficacy	9 (24.3)
Difficulty with dosing	7 (18.9)
Adverse event	17 (45.9)
Not known	4 (10.8)
Ezetimibe changes	16
Lack of efficacy	2 (12.5)
Difficulty with dosing	3 (18.8)
Adverse event	8 (50.0)
Not known	3 (18.8)
Fibrate changes due to lack of efficacy	3 (100.0)

IQR interquartile range

[a]Unless otherwise stated; not all variables were available for all patients

[b]Includes cholestyramine ($n=2$), colesevelam ($n=2$), evolocumab ($n=1$), omega 3 ($n=4$), and not known ($n=2$)

[c]Equivalent daily dose

[d]Rosuvastatin 5 mg twice weekly ($n=2$); rosuvastatin 5 mg three times/week ($n=1$); rosuvastatin 5 mg regimen, and other (not specified; $n=2$)

[e]Categories captured for reason for discontinuation were: 'difficulty with dosing,' 'due to adverse event,' 'due to lack of efficacy,' and 'not known.' For brevity, results where no data were present are not shown

to 150 mg and then subsequently down-titrated to 75 mg. Although not explicitly investigated in this study, it is the opinion of the authors that dosing flexibility and ability to adjust strength based on response and acceptability are important when initiating a new treatment. Additionally, the fact that several patients remained on a lower strength of alirocumab (despite high LDL-C at initiation) may reflect the high level of statin intolerance observed and patient and/or physician preference in initiating any new medications at lower strengths in an attempt to mitigate potential side effects. Finally, low rates of alirocumab discontinuation were observed; however, this was determined over a relatively short follow-up period.

4.1 Limitations

The study was designed to capture data that accurately represent the real-world UK population receiving alirocumab to inform future discussions with HTA bodies. Thus, this study was descriptive only, and no formal power calculations of outcomes were conducted; nevertheless, observations of

Table 3 Alirocumab prescribing patterns during the post-initiation period

Variable	Cohort ($N=150$)[a]
Starting strength of alirocumab, *n* (%)	
75 mg	108 (72.0)
150 mg	42 (28.0)
Alirocumab strength change, *n* (%)	
75 mg → 150 mg	35 (23.3)[b]
150 mg → 75 mg	0 (0.0)
75 mg → 150 mg → 75 mg	2 (1.3)
Time to up-titration of alirocumab, *n*	35
Weeks, median (range; IQR)	11.7 (4.0–16.0; 8.0–12.9)
Alirocumab discontinuation, n (%)	19 (12.7)
Reason	–
Lack of efficacy	0 (0.0)
Difficulty with dosing	0 (0.0)
Adverse event (patient or physician reported)	17 (89.5)
Not known	2 (10.5)
Change in background statin treatment, *n* (%)	42
No change	34 (81.0)
Discontinuation	5 (11.9)
Initiation	3 (7.1)
Change in background ezetimibe treatment, *n* (%)	60
No change	56 (93.3)
Discontinuation	1 (1.7)
Initiation	3 (5.0)
No change in background fibrate treatment, *n* (%)	8 (100.0)

IQR interquartile range

[a]Unless otherwise stated; not all variables were available for all patients

[b]Includes two patients who were subsequently down-titrated to 75 mg

potential interest to prescribers and decision-makers have been discussed herein.

As with any retrospective observational study based on secondary data, interpretation of study end points relies on the completeness and quality of the source medical records and accuracy of data abstraction from medical records available in routine NHS practice. Furthermore, retrospective observational studies can be limited by real-world-related biases with numerous (potentially unmeasurable) confounders. Efforts were sought to ameliorate these limitations by testing for potential between-center bias, recruiting patients in reverse consecutive order, and employing source data verification to enable correction of abstraction errors.

To minimize bias and to reflect, as accurately as possible, a cross-section of clinical experience throughout the UK, sites were chosen from different geographical locations across England, Wales, and Scotland that regularly prescribed alirocumab. Therefore, the characteristics of patients treated with alirocumab at centers that were not regular prescribers may be different from those included in this study. Additionally, to recruit enough patients, most data were derived from the central region of England, where alirocumab use has been most prevalent since the implementation of HTA body recommendations. Demographics in this area may be different from other UK regions; however, patient numbers were too small to establish this. Larger studies are required to increase the generalizability of the data.

The relatively short follow-up period of 4 months was implemented because of the slow uptake of PCSK9i observed across the UK [22] and the short time frame between publication of HTA body recommendations and study recruitment. Longer term follow-up is warranted to observe clinical outcomes with alirocumab.

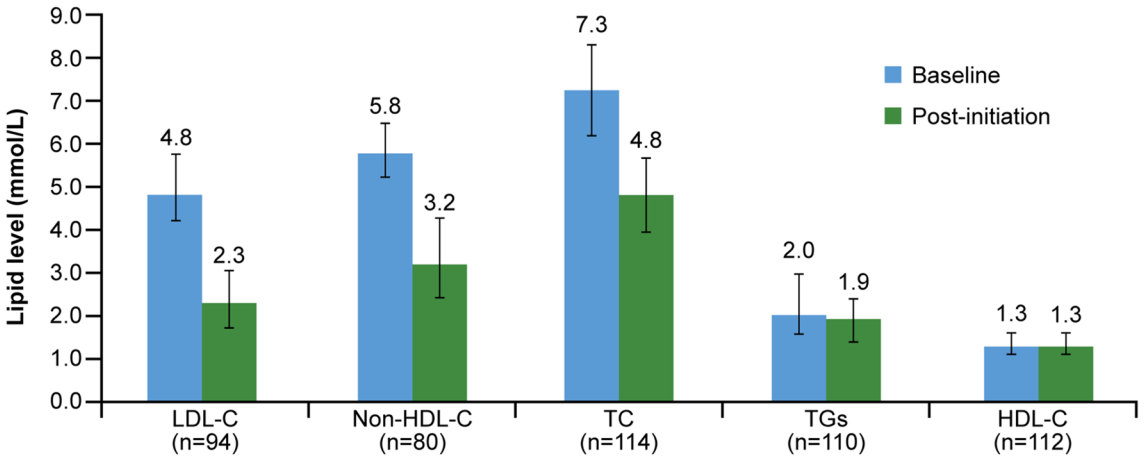

Fig. 1 Change in lipid parameters over the post-initiation period. *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride. Bars and error bars record the median and interquartile range, respectively. Data reported for all patients for whom a paired lipid parameter measurement were available before any changes in alirocumab dose

Table 4 Change in lipid parameters from baseline

	LDL-C	Non-HDL-C	TC	TG	HDL-C
All[a]					
n	94	80	114	110	112
Median (IQR) change from baseline (%)	− 53.6 (− 62.9 to − 34.9)	–45.7 (–53.8 to –30.1)	− 34.7 (− 42.8 to − 23.5)	− 9.8 (− 29.6 to 15.1)	4.9 (− 6.3 to 13.7)
P value	< 0.001	< 0.001	< 0.001	0.004	0.002
75 mg[b]					
n	64	52	82	78	80
Median (IQR) change from baseline (%)	− 50.0 (− 60.0 to − 32.8)	–42.5 (− 52.7 to − 28.5)	− 31.8 (− 41.7 to − 21.3)	− 8.9 (− 32.4 to 15.1)	1.7 (–6.3 to 14.6)
P value	< 0.001	< 0.001	< 0.001	0.016	0.022
150 mg[c]					
n	30	28	32	32	32
Median (IQR) change from baseline (%)	− 60.2 (− 69.8 to 50.3)	− 49.0 (− 57.3 to − 39.4)	− 40.0 (− 47.9 to − 34.5)	− 10.5 (− 27.7 to 16.2)	7.9 (− 1.6 to 13.3)
P value	< 0.001	< 0.001	< 0.001	0.104	0.041

HDL-C high-density lipoprotein cholesterol, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

[a]All patients for whom a paired lipid parameter measurement was available before any changes in alirocumab dose

[b]Patients who started on the 75 mg strength of alirocumab and remained on 75 mg at the time the post-initiation lipid parameter measurement was taken

[c]Patients who started on the 150 mg strength of alirocumab and remained on 150 mg at the time the post-initiation lipid parameter measurement was taken

The summary measures reported represent the median (IQR) of percentage changes at a patient level. The Wilcoxon signed rank test was used to generate *P* values

The study was not statistically powered to estimate effectiveness of alirocumab regarding change in lipid parameters and, unexpectedly, paired data were not available for all patients, resulting in small sample sizes for evaluation. The lack of LDL-C data for some patients was mostly due to concurrent hypertriglyceridemia (> 4.5 mmol/l) ,which would confound the calculation of LDL-C via the Friedewald equation. Additionally, follow-up blood tests in some centers may not have been conducted for some patients within 6 months of initiation. Furthermore, lipid parameter changes may have been confounded by changes to background LLT regimens, which we were unable to adjust for given the paucity of recorded changes observed in routine clinical practice. Furthermore, treatment adherence with alirocumab was not captured. Lastly, although reflective of early alirocumab use in the UK, lipid parameter changes reported pertain primarily to HeFH patients with statin intolerance and limited representation from those with primary non-familial hypercholesterolemia or mixed dyslipidemia.

Data regarding individual AE terms, severity grading, and their duration were not collected because of the anticipated incomplete and inconsistent recording of this information in medical records across sites in routine practice. However, the safety profile of alirocumab was well described during the ODYSSEY clinical trial program [11].

5 Conclusion

Early use of alirocumab predominantly in high-risk patients with HeFH and patients with a high level of statin intolerance indicates an unmet need for the treatment of hyperlipidemia inadequately controlled with conventional LLT use.

The high degree of alirocumab 75 mg usage suggests that two strength flexibility is an important attribute of this novel therapeutic option in clinical practice. Additionally, although the study was designed to be descriptive only, low discontinuation and clinically significant LDL-C reductions are supportive of the utility of alirocumab in clinical practice.

Acknowledgements The authors thank all investigators involved in this study. This study was sponsored and funded by Sanofi. We thank OPEN VIE (formerly pH Associates) for providing the statistical and analytical execution of this study. Medical writing assistance and editorial support, under the direction of the authors, were provided by Samantha Webster, BSc (Hons), and Kate Carolan, PhD, of Prime (Knutsford, UK), funded by Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869). The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication. Praluent® was developed in collaboration with Sanofi and Regeneron Pharmaceuticals.

Funding This study was funded by Sanofi. Medical writing assistance and editorial support were funded by Sanofi according to Good Publication Practice guidelines.

Compliance with Ethical Standards

Conflict of interest T. Reynolds has received project grants and personal fees from Genzyme Therapeutics (now Sanofi Genzyme), Shire Pharmaceuticals (now Takeda), and Synageva BioParma (now Alexion Pharma UK); payment for lectures from Sanofi, Shire (now Takeda), and AstraZeneca. P. Carey has received honorarium and personal fees from Sanofi. J. George has no conflicts of interest to declare. G. Konidaris is an employee of Sanofi. D. Narayanan has received honoraria from Sanofi. S. Ramachandran has received honoraria from Sanofi, Novo Nordisk, Napp, Janssen, AstraZeneca, Besins Healthcare; educational grants from Sanofi and Besins Healthcare; and a research grant from Bayer PLC. L Saunders is an employee of OPEN VIE (formerly pH Associates), which has been funded by Sanofi for the statistical and analytical execution of this study. L. Saunders has no other conflicts of interest to declare. A. Viljoen has received funding and/or conducted research studies funded by AstraZeneca, Boehringer Ingelheim, Amgen, Novo Nordisk, Napp, Janssen, Eli Lily, and Sanofi Aventis. G. Ferns has received grants, non-financial support, and other fees from Sanofi; and other fees from Amgen.

Research involving human participants Anonymized patient-level data, corresponding to a predefined core data set, were collected from electronic medical notes and paper charts and entered into a database. The database used was compliant with the Code of Federal Regulations 21 (Part 11) and approved for use in the National Health Service (NHS) setting. The study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice 19, in accordance with local regulations, including local data protection regulations.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Cholesterol Treatment Trialists Collaboration, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81. https://doi.org/10.1016/s0140-6736(10)61350-5.
2. Armitage J, Baigent C, Barnes E, Betteridge DJ, Blackwell L, Blazing M, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393(10170):407–15. https://doi.org/10.1016/S0140-6736(18)31942-1.
3. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97. https://doi.org/10.1056/NEJMoa1410489.
4. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22. https://doi.org/10.1056/NEJMoa1615664.
5. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–107. https://doi.org/10.1056/NEJMoa1801174.
6. Defesche JC, Stefanutti C, Langslet G, Hopkins PN, Seiz W, Baccara-Dinet MT, et al. Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia. J Clin Lipidol. 2017;11(6):1338–46e7. https://doi.org/10.1016/j.jacl.2017.08.016.
7. Hartgers ML, Defesche JC, Langslet G, Hopkins PN, Kastelein JJP, Baccara-Dinet MT, et al. Alirocumab efficacy in patients with double heterozygous, compound heterozygous, or homozygous familial hypercholesterolemia. J Clin Lipidol. 2018;12(2):390-6e8. https://doi.org/10.1016/j.jacl.2017.12.008.
8. Glerup S, Schulz R, Laufs U, Schlüter K-D. Physiological and therapeutic regulation of PCSK9 activity in cardiovascular disease. Basic Res Cardiol. 2017;112(3):32. https://doi.org/10.1007/s00395-017-0619-0.
9. Sanofi-Aventis Groupe. Summary of product characteristics. Praluent 150 mg solution for injection in pre-filled pen. 2018. https://www.medicines.org.uk/emc/product/8093/smpc. Accessed 22 Feb 2019.
10. Weinreich M, Frishman WH. Antihyperlipidemic therapies targeting PCSK9. Cardiol Rev. 2014;22(3):140–6. https://doi.org/10.1097/crd.0000000000000014.
11. Roth EM. Alirocumab for low-density lipoprotein cholesterol lowering. Future Cardiol. 2019;15(1):17–29. https://doi.org/10.2217/fca-2018-0072.
12. National Institute for Health and Care Excellence. TA393: alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. 2016. https://www.nice.org.uk/guidance/ta393. Accessed 22 Feb 2019.
13. Scottish Medicines Consortium. 1147/16: alirocumab (Praluent). 2016. https://www.scottishmedicines.org.uk/medicines-advice/alirocumab-praluent-fullsubmission-114716/. Accessed 22 Feb 2019.
14. Peers K, Ramachandran S, Syed A, Jones A, editors. A comparison of the efficacy and tolerability of the PCSK9 inhibitors, alirocumab and evolocumab, in routine lipid clinic practice. In: 31st Heart UK Annual Medical and Scientific Conference; 2017; Warwick, UK.
15. Kohli M, Patel K, MacMahon Z, Ramachandran R, Crook MA, Reynolds TM, et al. Pro-protein subtilisin kexin-9 (PCSK9) inhibition in practice: lipid clinic experience in 2 contrasting UK centres. Int J Clin Pract. 2017;71(11):e13032. https://doi.org/10.1111/ijcp.13032.
16. Johri N, Cabrera-Abreu J, Livingstone C, Loli Y, Malik M, Maghsoodi N et al. Real world use of PCSK9 inhibitors in lipid clinics in SE England. HEART UK 2019; 3–5 July, 2019; Coventry, UK 2019.
17. Government Publishing Office. Electronic Code of Federal Regulations. Title 21: food and drugs. Part 11—electronic records; electronic signatures. 2019. https://www.ecfr.gov/cgi-bin/text-idx?SID=13be62008614e7a8c1d1421364a891e3&mc=true&node=pt21.1.11&rgn=div5. Accessed 22 Feb 2019.
18. World Medical Association. WMA Declaration of Helsinki—Ethical principles for medical research involving human subjects. 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 22 Feb 2019.
19. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). 2015. https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed 22 Feb 2019.
20. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is

underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478–90a. https://doi.org/10.1093/eurheartj/eht273.
21. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J. 2015;36(43):2996–3003. https://doi.org/10.1093/eurheartj/ehv370.
22. NHS Digital. Estimates of predicted use compared to observed use. 2018. https://files.digital.nhs.uk/6B/C010A1/nice-tech-apps-eng-oct18-inno-scor-est.pdf. Accessed 11 Mar 2019.

Affiliations

Tim Reynolds[1] · Peter Carey[2] · Jacob George[3] · Gerasimos Konidaris[4] · Deepa Narayanan[5] · Sudarshan Ramachandran[6] · Luke Saunders[7] · Adie Viljoen[8] · Gordon Ferns[9]

1 Queen's Hospital, Burton-on-Trent, UK
2 Sunderland Royal Hospital, Sunderland, UK
3 Ninewells Hospital, Dundee, UK
4 Sanofi UK, Guilford, UK
5 Hull and East Yorkshire Hospitals NHS Trust, Hull, UK
6 Good Hope Hospital/Birmingham Heartlands Hospital, Sutton Coldfield, UK
7 OPEN VIE, Marlow, England, UK
8 Lister Hospital, Stevenage, UK
9 Brighton and Sussex University Hospital, Brighton BN1 9PX, UK